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In the claims:

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Sub H1 >
10. (Twice Amended) A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein the truncated polypeptide is a derivative of a glycoprotein of a herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex type 1 and/or type 2.

REMARKS

Applicants thank the Examiner for the withdrawal of the rejections under Sections 112, second paragraph, 102, and 103.

For the Examiner's convenience, the pending claims are attached in an Appendix. Claim 10 has been amended to be in correspondence with the allowed claims of the parent application to this case, Serial No. 08/357,084.

Applicants acknowledge the Examiner's remarks concerning the consideration of the art set forth on the PTO-1449 Forms. Applicants understand that the Examiner is in the process of locating and re-ordering the publications which were not crossed out and does intend to consider all of the art. Regarding the EPO publication of which the Examiner does not have a copy and which she reports to not be in the parent files, Applicants will forward this publication when it has been retrieved.

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Applicants understand Claims 11, 18 and 19 to be allowable if rewritten in independent form.

The Provisional Double Patenting Rejections (Paragraphs 4 and 6 of Paper No. 11)

Applicants note the Examiner's acknowledgment that Applicants would consider the filing of a terminal disclaimer sanctioned by 37 C.F.R. § 1.321 if appropriate at the time claims of the present case are found allowable but for this issue. Regarding the provisional rejections under the Examiner's New Grounds of Rejection, Applicants will also handle this matter at the time of allowable subject matter. Similarly, Applicants add that they will also handle the issues under Section 101 regarding Claims 10-23 at the time of any allowable subject matter.

The Rejection under 35 U.S.C. § 112, First Paragraph (Paragraph 5 of Paper No. 10)

Claims 10, 12, 13-17 and 20-23 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is purportedly "only enabling for claims limited to a method of producing a glycoprotein D vaccine and a vaccine containing the glycoprotein D of the herpes simplex virus". Particularly, the Examiner states that Applicants' arguments are unpersuasive because the Declaration of Dr. Rose states that a glycoprotein must not only raise antibodies against a pathogen, but it must be protective. The Examiner further states that "[t]his protection was not shown for glycoprotein C or B or any combination of glycoproteins." The Examiner goes on

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to state that "[t]here is no description or enablement in any declaration for a glycoprotein B or C or a mixture of glycoproteins". The Examiner also points to page 7 of an EPO decision, Exhibit F filed with Applicants' 5 February 1997 amendment, which distinguishes against prior art by showing that the prior art does not show immunogenicity data. Applicants respectfully traverse.

Applicants submit the following three lines of argument. First, as previously submitted, the facts surrounding the present disclosure differ from the facts concerning the art cited by the Examiner, and therefore, the same conclusions applied to the art cited by the Examiner cannot be applied to the presently claimed subject matter. However, importantly, and apparently not previously addressed with persuasiveness, the second point addressed herein is that the Declarations submitted in Applicants' 5 February 1997 Amendment do support the presently claimed subject matter, in contrast to the Examiner's statements. In particular, they specifically address the protective immunogenicity conferred by "derivatives of a herpes glycoprotein", as recited in Claims 10-23. The third issue addressed herein is a confirmation study (Exhibit A) performed by others after the filing of the first application from which the present application descends, which shows that all of the statements in the present application are true, and thus, one skilled in the art would have reasonably expected to practice the claimed invention at the time of filing the first application from which the present application descends given the specification.

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The facts regarding the other art and the present invention differ

A recurring theme throughout the prosecution of this case has been that because challenge data was necessary for the skilled artisan to have a reasonable expectation of success in practicing the disclosures of Watson and Rose, then challenge data is necessary to establish patentability of the present invention. However, the facts surrounding Watson, Rose and the comments made in the EPO decision referred to by the Examiner, differ from the facts surrounding the present invention. Therefore, the same conclusions cannot be applied to all of these cases without a careful analysis.

In vivo data exists in the present case, not the other art

Analysis of the present case shows that there is *in vivo* data, for glycoprotein D. This successful challenge data not only enables the invention for glycoprotein D, but enables the full scope of the claims. Specifically, this data changes the predictability of the claimed vaccines from that of the vaccines suggested in Watson or Rose, which showed only *in vitro* data, and for different expression products. Therefore, given the specification of the present invention, which includes successful *in vivo* data, one skilled in the art would have a reasonable expectation of success in practicing the claimed invention, over the full scope of the claims.

The other art in vitro data suggested problems

In addition to the *in vivo* data provided by the present disclosure, there are other reasons which distinguish the present case from Watson and Rose in regards to the enablement issue. Watson discloses the expression of fusion proteins, and Rose discloses a truncated glycoprotein G protein that could be folded into "an unusual

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confirmation". In both disclosures, there appeared to be doubt as to whether the disclosed peptides would be effective against a challenge. In particular, as repeatedly pointed out by Applicants, the authors in Watson declared that further experimentation was necessary to determine the capabilities of the fusion peptides. The authors in Rose were clearly perplexed by the folding patterns. Therefore, it was clear that challenge data was necessary for these particular cases in order to be sufficiently enabled to support the obviousness rejections. In contrast, the present application suggests no such problems, but rather presents a combination of successful *in vivo* and *in vitro* data.

The present disclosure provides further support

The present disclosure further differs from Watson and Rose because Applicants have provided similarities between glycoprotein C and the protein which has been specifically demonstrated to be successful as a vaccine, glycoprotein D. Namely, page 46, lines 19-28 show that sequence comparisons of glycoproteins C and F demonstrate that the carboxy-terminal transmembrane domains of these proteins are able to tolerate a large number of mutations in this area so long as the substituted amino acids are hydrophobic. These results are similar to those found for the glycoprotein D genes of HSV-1 and HSV-2. Another similarity is that all of the glycoproteins possess some type-common determinants (page 2, lines 29-32). In contrast, the disclosures of Watson and Rose were severely limited to *in vitro* data fraught with problems.

In conclusion, the disclosures of Watson or Rose and the present invention are not the same, and therefore, the same conclusions cannot be drawn. The cases must be looked at on an individual basis, each as a whole. Given the complete

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disclosure of the present application wherein *in vivo* data is presented, Applicants submit that each and every one of the presently claimed vaccines do not require challenge data to be enabled. The Declarations and Exhibit A discussed below, fully support these assertions.

The Declarations are supportive of the full scope of the claims

It is Applicants' position that the Declarations submitted throughout prosecution of the lineage of this case, and specifically in this case with the Amendment filed 5 February 1997, appear to have not been carefully considered or given the weight to which they are worthy. As previously indicated, these Declarants are not inventors of the present invention, and in fact, Dr. Rose is an author of one of the publications previously cited against the present invention by the Examiner. The Official Action only makes one reference to Dr. Rose's First Declaration, which does not reflect the sentiments of the Declaration as a whole. Moreover, the Official Action states that the Declarations support glycoprotein D, when in fact, they support vaccines comprising truncated polypeptides which are derivatives of a herpes glycoprotein.

The claims currently pending are limited to vaccines comprising truncated polypeptides which are derivatives of a herpes glycoprotein of a herpes simplex virus type 1 or type 2, wherein the pathogen they are capable of raising neutralizing antibodies against is herpes simplex type 1 and/or type 2. This subject matter is well within the boundaries of the subject matter which is attested to in the Declarations as conferring protective immunity.

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The First Declaration of Dr. Rose

The Examiner cited the First Declaration of Dr. Rose (Exhibit A in the Amendment of 5 February 1997), for the proposition that "that an antigen must not only raise antibodies against a pathogen, but it must be protective". Applicants point out that Paragraph 9 of the same Declaration goes on to state:

Based upon this pioneering demonstration with the herpes simplex vaccine model, their results provide a reasonable expectation that the system would be successful with other viral pathogens.
(Emphasis added).

The use of the phrase "herpes simplex vaccine model" implies that the demonstration is applicable beyond glycoprotein D. The term "successful" indicates that the vaccines based on the presented "model" would be protective. The use of the term "pioneering", indicates that Dr. Rose envisioned ground breaking and broad applications with this system. Therefore, Applicants submit that Dr. Rose's First Declaration supports the claimed invention, drawn to vaccines comprising truncated polypeptides which are derivatives of a herpes glycoprotein of a herpes simplex virus type 1 or type 2, wherein the pathogen they are capable of raising neutralizing antibodies against is herpes simplex type 1 and/or type 2.

The Second Declaration of Dr. Rose

Moreover, the Second Declaration of Dr. Rose (submitted as Exhibit B in the Amendment of 5 February 1997), also supports the full scope of the claims. In paragraph 6, Dr. Rose refers to the invention as providing "protection against a pathogen based solely on a truncated, membranc-free derivative of a viral glycoprotein," again indicating that one skilled in the art does not consider the invention limited to glycoprotein D or a specific pathogen (emphasis added).

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Moreover, this language shows that Dr. Rose believes these glycoproteins to confer protection. This language directly reads on Claim 10, from which all of the pending claims depend. Therefore, this Declaration supports the full scope of the claims.

Moreover, in Paragraph 13 of this Declaration, Dr. Rose explains that any reasonable expectations of success in using the disclosed system arose because the inventors "demonstrated that all of the technical challenges to successful vaccine production had been overcome". Applicants, therefore, again, submit that this Declaration supports enablement of the claimed invention.

Declaration by David S. Secher

Lastly, the Declaration by David S. Secher, previously submitted as Exhibit C in the Amendment of 5 February 1997, supports the scope of the claims. Paragraph 11 of the this Declaration states:

The scientific strength of this research resides in the use of a truncated version of a single glycoprotein from the rather complex model Herpes Simplex virus to confer protective immunity in the animal against the pathogen. (Emphasis added).

Applicants, point out that like Dr. Rose, Dr. Secher did not mention the use of glycoprotein D, but rather, refers generally to a truncated version of a glycoprotein. Moreover, this Declaration specifically states that the glycoprotein does "confer protective immunity". Applicants, therefore, submit that this Declaration supports enablement of the claimed invention, particularly that the claimed glycoproteins confer protective immunity and therefore function as vaccines.

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The assertions in the Application have been confirmed

Applicants submit herein a study which shows that the claimed vaccines do in fact confer protective immunity, Exhibit A, Ghiasi, et al., *J. Virol.*, 68(4):2118-2126 (1994). While Exhibit A was published well after the filing of the first application from which the present application descends, it has relevance for the following reasons. First, while the study claims to be the first to express many herpes glycoproteins in baculovirus so that large quantities of the glycoproteins can be produced for study, the study makes clear that all of the glycoproteins which are being reported on have previously been studied and shown to be immunogenic, (page 2123, left column, first line of the second full paragraph). (Of note, of the "previous studies" which are referenced in Exhibit A, is a paper by Berman, (reference 4), the first named inventor of the present invention). Second, Exhibit A is relevant to show that the assertions reasonably made in the application are in fact true, thus the claims are enabled.

Applicants submit that once the present disclosure showed the protective immunity of glycoprotein D, this changed the state of the art from that of the time of Watson and Rose. The publications of Watson and Rose displayed uncertainty and doubt. However, with the showing of protective immunity for glycoprotein D began a new era in the study of vaccines against herpes simplex type 1 and/or type 2. Thus, the positive challenge data, coupled with the expression of glycoprotein C and the rest of the data disclosed in the specification, gave for the first time to those skilled in the art, a reasonable expectation of practicing the claimed invention. As Exhibit A demonstrates, one skilled in the art can in fact practice the claimed invention with success.

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The Examiner has not presented a *prima facie* case for non-enablement of the present claims since Watson and Rose differ significantly in background and facts from the present invention. Moreover, any doubt of the truth of the statements in the application is rebutted by Exhibit A which shows that the claims are in fact enabled, in that the claimed vaccines do confer protective immunity. Moreover, the Declarations show that one skilled in the art would expect, given the present disclosure at the time of filing the first application from which this application descends, that the claimed vaccines would confer protective immunity. Applicants respectfully point out that rejections can be overcome by suitable proofs such as the submission of expert declarations. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Therefore, Applicants respectfully request that the rejection be withdrawn.

Conclusion

Given all the foregoing statements, Applicants submit that the present specification is enabling for all of the claimed vaccines. In light of the disclosure which provides a combination of *in vivo* and *in vitro* data and consideration of the previously submitted evidentiary Declarations and Exhibit A enclosed herein, Applicants respectfully request withdrawal of the outstanding rejection. In particular, two experts in the field, non-inventors of the present application, attest to their belief that the claimed glycoproteins would confer protective immunogenicity given the first disclosure from which this application descends. The Examiner has not presented any evidence as to why these declaratory statements should be

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doubted. Moreover, Exhibit A demonstrates that the claimed vaccines do in fact confer protective immunity.

From all of the prosecution history which spans over a dozen years, we believe that it must be concluded that the review of patentability standards for the present claimed subject matter has been thorough and complete enough to induce the Patent Office's production of an official notice of allowance. We respectfully request this.

Respectfully submitted,

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